

**WEST**

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L2: Entry 10 of 14

File: DWPI

Jul 9, 1996

DERWENT-ACC-NO: 1996-368115

DERWENT-WEEK: 199637

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TITLE: Cell adhesion inhibitor used as immunosuppressant -  
contains plants or their extracts of e.g. stellaria neglecta,  
artemisia capillaris and/or isodon japonicus

PATENT-ASSIGNEE:

ASSIGNEE

CODE

KAO CORP

KAOS

PRIORITY-DATA:

1994JP-0325334

December 27, 1994

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
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APPLICATION-DATA:

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INT-CL (IPC): A61K 35/78

ABSTRACTED-PUB-NO: JP08176002A

BASIC-ABSTRACT:

Cell adhesion inhibitors contain one or more plants or their extracts from *Stellaria neglecta*, *Aquarimonia pilsoa*, *Hydrangea macrophylla*, *Artemisia capillaris*, *Euphorbia kansui*, *Agastache rugosa*, *Glechoma hederacea*, *Matricaria chamomilla*, *Euphorbia lathyris*, *Spirodela ployrhiza*, *Mentha haplocalyx* and *Isodon japonicus*.

EMBODIMENT - Plants are opt. dried and extracted with water and/or organic solvent(s) (e.g. hydrocarbons, ethers, esters, and alcohols). The extract is evaporated to give powder or paste. The prod. is used to prepare pharmaceutical preps. using other additives.

USE - The inhibitor is used in an amt.of 0.0001-40 (pref. 0.01-20) wt.% as dried solid mass and 20-500 mg/kg/day.

ADVANTAGE - The inhibitor has low cytotoxicity. Inhibitor is used to treat cancer metastasis and as an antiallergic agent and immunosuppressant.

EXAMPLE - In an example, extracts of plants inhibited adhesion of cancer cells at rates of 92, 98, 80, 84, 92, 98, 76, 78, 84, 97 and 82% respectively at a concn. of 0.001% to vascular endothelial cells.

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: CELL ADHESIVE INHIBIT IMMUNOSUPPRESSIVE CONTAIN  
PLANT EXTRACT ARTEMISIA ISODON JAPONICA

DERWENT-CLASS: B04

CPI-CODES: B04-A08C2; B04-A10; B14-G02; B14-H01B;

CHEMICAL-CODES:

Chemical Indexing M1 \*01\*

Fragmentation Code

M423 M710 M903 P431 P433 P434 P633 V400 V404 V406

SECONDARY-ACC-NO:

CPI Secondary Accession Numbers: C1996-116253

**WEST**

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L2: Entry 2 of 14

File: JPAB

Jul 9, 1996

PUB-NO: JP408176002A  
DOCUMENT-IDENTIFIER: JP 08176002 A  
TITLE: CELL-ANCHORING INHIBITOR

PUBN-DATE: July 9, 1996

## INVENTOR-INFORMATION:

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N/A

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APPL-DATE: December 27, 1994

INT-CL (IPC): A61K 35/78; A61K 35/78; A61K 35/78; A61K 35/78;  
A61K 35/78

## ABSTRACT:

PURPOSE: To provide a cell-anchoring inhibitor, metastasis inhibitor, antiallergic agent and immunosuppressive agent containing, as active ingredients, the plants or extracts therefrom selected from the followings: *Stellaria neglecta*, *Agrimonia pilosa*, *Hydrangea macrophylla*, *Artemisiacapillaris*, *Euphorbia kansui*, *Agastache rugosa*, *Glechoma hederacea*, *Matricaria chamomila*, *Euphorbia lathyris*, *Spirodela ployrhiza*, *Mentha haplocalyx* and *Isodom japonicus*.

CONSTITUTION: This cell-anchoring inhibitor, metastasis inhibitor, antiallergic agent or immunosuppressive agent contains as active ingredients, the whole body, leaves, petioles, branch roots of the following plants, as they are, or dried, crushed or extracted products: *Artemisiacapillaris*, *Euphorbia kansui*, *Agastache rugosa*, *Glechoma hederacea*, *Matricaria chamomila*, *Euphorbia lathyris*, *Spirodela ployrhiza*, *Mentha haplocalyx* and *Isodom japonicus*. The extraction is

preferably carried out by extracting the crushed products the whole bodies or parts of these plants with water or an organic solvent at 3-70°C. This medicine can be widely used in treatment and prophylaxis for cancer, asthma, allergic rhinitis, gout, psoriasis, urticaria, rheumatism, pollinosis, periodontal diseases, ischemic reperfusion disorder, acute respiratory distress syndrome, autoimmune diseases, acute alveolar disorder and the like.

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L29 ANSWER 5 OF 5 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD  
AB JP 08176002 A UPAB: 19961124

Cell **adhesion** inhibitors contain one or more plants or their  
extracts from *Stellaria neglecta*, *Aquarimonia pilsoa*, *Hydrangea*  
*macrophylla*,

*Artemisia capillaris*, *Euphorbia kansui*, ***Agastache rugosa***  
, *Glechoma hederacea*, *Matricaria chamomilla*, *Euphorbia lathyris*,  
*Spirodela*

*polyrhiza*, *Mentha haplocalyx* and *Isodon japonicus*.

EMBODIMENT - Plants are opt. dried and extracted with water and/or  
organic solvent(s) (e.g. hydrocarbons, ethers, esters, and alcohols). The  
extract is evaporated to give powder or paste. The prod. is used to  
prepare pharmaceutical preps. using other additives.

USE - The inhibitor is used in an amt. of 0.0001-40 (pref. 0.01-20)  
wt.% as dried solid mass and 20-500 mg/kg/day.

ADVANTAGE - The inhibitor has low cytotoxicity. Inhibitor is used to  
treat cancer metastasis and as an antiallergic agent and  
immunosuppressant.

EXAMPLE - In an example, extracts of plants inhibited  
**adhesion** of cancer cells at rates of 92, 98, 80, 84, 92, 98, 76,  
78, 84, 97 and 82% respectively at a concn. of 0.001% to vascular  
endothelial cells.

Dwg. 0/0

ACCESSION NUMBER: 1996-368115 [37] WPIDS

DOC. NO. CPI: C1996-116253

TITLE: Cell **adhesion** inhibitor used as  
immunosuppressant - contains plants or their extracts of  
e.g. *stellaria neglecta*, *artemisia capillaris* and/or  
*isodon japonicus*.

DERWENT CLASS: B04

PATENT ASSIGNEE(S): (KAOS) KAO CORP

COUNTRY COUNT: 1

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(54) 【発明の名称】 細胞接着抑制剤

(57) 【要約】

【構成】 ハコベ草、仙鶴草、甘茶、茵陈蒿、甘遂、カッコウ、連銭草、カミツレ、千金子、浮き草、薄荷及び延命草から選ばれる1種もしくは2種以上の植物又はその抽出物を有効成分とする細胞接着抑制剤、癌転移抑制剤、抗アレルギー剤又は免疫抑制剤を提供するものである。

【効果】 細胞毒性が低く、細胞接着抑制作用、抗アレルギー作用、癌転移抑制作用、免疫抑制作用に優れる。

## 【特許請求の範囲】

【請求項1】 ハコベ草、仙鶴草、甘茶、茵陳蒿、甘遂、カッコウ、連銭草、カミツレ、千金子、浮き草、薄荷及び延命草から選ばれる1種もしくは2種以上の植物又はその抽出物を有効成分とする細胞接着抑制剤。

【請求項2】 請求項1記載の植物又はその抽出物を有効成分とする癌転移抑制剤。

【請求項3】 請求項1記載の植物又はその抽出物を有効成分とする抗アレルギー剤。

【請求項4】 請求項1記載の植物又はその抽出物を有効成分とする免疫抑制剤。

## 【発明の詳細な説明】

## 【0001】

【産業上の利用分野】本発明は、植物又はその抽出物を有効成分とする細胞接着抑制剤、癌転移抑制剤、抗アレルギー剤及び免疫抑制剤に関する。

## 【0002】

【従来の技術】従来、抗炎症剤としては、ステロイド剤、アラキドン酸代謝物や、ヒスタミン等に代表される化学伝達物質の産生・放出抑制剤、レセプター拮抗剤などが広く用いられている。また、免疫抑制剤としてはアザチオプリン、ミゾリビン等の代謝拮抗剤、プレドニゾン等のステロイド剤、各種抗体、サイクロスポリン、FK506等が用いられている。そして、癌転移抑制剤として有効な物質は未だ見出されていない。

【0003】一方、近年各種の炎症、免疫反応、癌転移についての分子レベルでの研究が進展し、これらの疾患には共通して白血球と血管内皮細胞、癌細胞と血管内皮細胞などの細胞間接着が大きく関与していることが明らかとなり、接着に携わる細胞接着分子そのものの発現抑制や接着分子のマスキングなどによる細胞間の接着抑制が、上記疾患の治療に有効であることが明らかになりつつある〔「接着分子の発現調節と臨床応用」(メジカルビュー社、1991年)、Nature, Vol. 364, 149-155 (1993)、Science, Vol. 247, 456-459 (1990)、Annual Review免疫1989, 175-185、Trends in Glycoscience and Glycotechnology, Vol. 4, No. 19, 405-414 (1992)、実験医学 Vol. 10, No. 11, 1402-1413 (1992)、実験医学 Vol. 11, No. 16, 2168-2175 (1993)、Science, Vol. 255, 1125-1127 (1992)等〕。そして、細胞間の接着にはICAM-1, ELAM-1, VCA M-1等の細胞表面接着分子が関与していることが明らかになっている〔Annual Review免疫1989, 175-185、感染・炎症・免疫Vol. 19 (2), 129-153 (1989)、感染・炎症・免疫Vol. 24 (3), 158-165 (199

4)〕。

【0004】これらの細胞接着を抑制する物質としては細胞表面接着分子に対する抗体やリガンド、N-(フルオレニル-9-メトキシカルボニル)アミノ酢酸、3-デアザアデノシン等が知られているが〔Proc. Natl. Acad. Sci. USA, Vol. 88, 355-359 (1991)、Immunopharmacology, 23, 139-149 (1992)、J. Biological Chemistry, Vol. 267 (13), 9376-9382 (1992)、J. Immunology, Vol. 144 (2), 653-661 (1990)〕、その効力は未だ満足できるものではなかった。

## 【0005】

【発明が解決しようとする課題】従って本発明の目的は、この細胞接着を有効に抑制する薬物、更に抗アレルギー剤、免疫抑制剤及び癌転移抑制剤を提供することにある。

## 【0006】

【課題を解決するための手段】斯かる実情に鑑み本発明者は、種々の植物抽出物等について細胞接着抑制作用を検討し、癌モデルを用いた試験を数多く行った結果、下記に示す植物が、意外にも優れた細胞接着抑制作用を有し、抗アレルギー剤、免疫抑制剤、癌転移抑制剤として有用であることを見出し本発明を完成した。

【0007】すなわち本発明は、ハコベ草、仙鶴草、甘茶、茵陳蒿、甘遂、カッコウ、連銭草、カミツレ、千金子、浮き草、薄荷及び延命草から選ばれる1種もしくは2種以上の植物又はその抽出物を有効成分とする細胞接着抑制剤、癌転移抑制剤、抗アレルギー剤及び免疫抑制剤を提供するものである。

【0008】本発明で用いる植物は、ハコベ草(ラテン名Stellaria neglecta)、仙鶴草(Agrimonia pilosa)、甘茶(Hydangea macrophylla)、茵陳蒿(Art emisiacapillaris)、甘遂(Euphorbia kansui)、カッコウ(Agastache rugosa)、連銭草(Glechoma hederacea)、カミツレ(Matricaria chamomilla)、千金子(Euphorbia lathyris)、浮き草(Spirodela ployrhiza)、薄荷(Mentha haplocalyx)及び延命草(Isodon japonicus)から選ばれるものである。本発明においては斯かる植物の全草又は葉、葉柄、枝根等が利用でき、これはそのまま又は乾燥して用いてもよい、粉碎し、更に抽出物を用いてもよい。

【0009】抽出方法は、植物の一部又は全体の粉碎物を通常3〜70℃で水又は有機溶媒により抽出する方法が挙げられる。ここで抽出に用いられる有機溶媒は、特に限定されないが例えば、石油エーテル、シクロヘキサン、トルエン、ベンゼン等の炭化水素類；四塩化炭素、ジクロロメタン、クロロホルム等のハロゲン化炭化水素；エーテル類；酢酸エチル等のエステル類；アセトン

等のケトン類；ブタノール、プロパノール、エタノール、メタノール、ポリエチレングリコール、プロピレングリコール、ブチレングリコール等のアルコール類；ビリジン等が挙げられる。抽出溶媒は単独で用いても2種以上を混合して用いてもよい。

【0010】得られた抽出物は、そのまま用いてもよいが、更に必要により濃縮、濾過、凍結乾燥等の処理をしたものを用いてもよい。また抽出物や植物体は単独でも2種以上を組み合わせて用いてもよい。

【0011】かくして得られる上記植物又はその抽出物は、優れた白血球-血管内皮細胞間に代表される細胞接着を抑制する作用を有する。更に優れた抗アレルギー作用、免疫抑制作用及び癌転移抑制作用を有する。更にまた、細胞毒性、皮膚刺激性等が弱く、安全性も高い。従って、上記植物又はその抽出物を有効成分として含有する医薬は、細胞接着抑制に基づき、歯周病、リウマチ、気管支喘息、花粉症、乾癬、虚血再灌流障害抑制、急性呼吸窮迫症候群、移植臓器拒絶反応抑制、自己免疫疾患等の治療及び癌転移予防に有用である。

【0012】上記植物又はその抽出物の医薬への配合量は、特に限定されないが、一般的に乾燥固形分に換算して0.0001~40重量%、特に0.01~20重量%とすることが好ましい。また1日の投与量は20mg/kg~500mg/kg/日とすることが好ましい。投与は、経口、経腸、外用等いずれの経路によってもよい。なおこれらの植物及びその抽出物の安全性は高いことが知られている。

【0013】本発明の医薬は上記必須成分の他、既存の抗炎症剤や抗アレルギー剤、抗ヒスタミン剤等の薬物と任意に組み合わせて配合、投与することができる。

【0014】剤形としては任意の形態をとることができ、例えば錠剤、散剤、顆粒剤、カプセル剤、坐剤、トロリー剤などの固形製剤、シロップ、乳液、軟ゼラチンカプセル、クリーム、ゲル、ペースト、スプレー、注射などの液状製剤が挙げられる。

【0015】これら剤形にするための賦形剤、その他の添加剤としては特に限定されず、例えば、固形状の物としては乳糖、カオリン、ショ糖、結晶セルロース、コーンスターチ、タルク、寒天、ペクチン、ステアリン酸、ステアリン酸マグネシウム、レシチン、塩化ナトリウムなどが挙げられ、液状のものとしてはグリセリン、落花生油、ポリビニルピロリドン、オリーブ油、エタノール、ベンジルアルコール、プロピレングリコール、水などが挙げられる。

【0016】本発明の医薬は常法により製造することができる。

【0017】

【発明の効果】本発明の医薬は、植物由来のため細胞毒性が低く、優れた細胞接着抑制作用、抗アレルギー作用、癌転移抑制作用、免疫抑制作用を有する。従って本

発明の医薬は癌、喘息、アレルギー性鼻炎、痛風、乾癬、じんましん、リウマチ、花粉症、歯周病、虚血再灌流障害、急性呼吸窮迫症候群、自己免疫疾患、急性肺胞障害等の予防、治療に広く用いることができる。

【0018】

【実施例】次に、実施例を挙げ本発明を更に詳細に説明するが、本発明はこれらに限定されるものではない。なお、以下の実施例で用いた植物抽出物は、次の方法により得た。乾燥ハコベ草1kgを、70%エタノール5リットルで、1週間室温で抽出し、70%エタノール可溶成分を得た。抽出液を分離した残渣について同様の操作を繰り返し、合計10リットルの抽出液を得た。この抽出液の溶媒を留去し減圧乾固し抽出物85gを得た。他の植物についても同様の操作により抽出物を得た。

【0019】実施例1

下記表1~3に示す如き植物抽出物を上記方法により得た。これら植物抽出物を下記の試験に供した。

(1)白血球-血管内皮細胞接着抑制試験：96穴培養プレート上にコンフルエントとなったヒト血管内皮細胞に対し、最終濃度〔乾燥固形分換算の重量%〕(以下同じ)0.001%となるように被験物質を添加する。18時間後にヒトIL-1 $\alpha$ を最終濃度2.5ng/mlとなるように添加し、6時間培養する。培養液除去後、新しい培養液で2回洗浄した後、予め<sup>51</sup>Cr標識したヒト末梢白血球10cells/mlを200 $\mu$ l添加し、培養する。30分後、未接着細胞を除去し、接着細胞を溶解後その放射活性を測定する。その結果を表1に示す。これからハコベ草、仙鶴草、甘茶、茵陳蒿、甘遂、カッコウ、連銭草、カミツレ、千金子、浮き草、薄荷、延命草は優れた細胞接着抑制活性を有することが判明した。

【0020】

【表1】

植物エキス	白血球接着抑制率(%)
ハコベ草	90
仙鶴草	95
甘茶	81
茵陳蒿	82
甘遂	95
カッコウ	79
連銭草	95
カミツレ	72
千金子	87
浮き草	80
薄荷	91
延命草	85

【0021】(2)癌細胞-血管内皮細胞接着抑制試験：96穴培養プレート上にコンフルエントとなったヒト血管内皮細胞に対し、最終濃度0.001、0.00



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0.1%となるように被験物質を添加する。18時間後にヒトIL-1 $\alpha$ を最終濃度2.5ng/mlとなるように添加し、6時間培養する。培養液除去後、新しい培養液で2回洗浄した後、予め $^{51}\text{Cr}$ 標識したヒト骨髄腫瘍細胞(HL-60)10cells/mlを200 $\mu\text{l}$ 添加し、培養する。30分後、未接着細胞を除去し、接着細胞を溶解後その放射活性を測定する。その結果を表2に示す。これよりハコベ草、仙鶴草、甘茶、茵陳蒿、甘遂、カッコウ、連銭草、カミツレ、千金子、浮き草、薄荷、延命草は癌細胞の転移に重要な、癌細胞と血管内皮細胞の接着を強く抑制することが判明した。

【0022】

【表2】

植物エキス	0.001%	0.0001%
	癌細胞接着抑制率(%)	
ハコベ草	92	48
仙鶴草	98	27
甘茶	80	5
茵陳蒿	84	10
甘遂	94	64
カッコウ	82	5
連銭草	98	30
カミツレ	76	5
千金子	78	38
浮き草	84	3
薄荷	97	8
延命草	82	5

【0023】(3)血管内皮細胞に対する毒性試験(細胞形態, DNA合成): 形態的变化に対しては倒立顕微鏡による目視判定とし、DNA合成は常法に従い $^3\text{H}$ -チミジンの取り込みを指標に、被験物質添加後24時間培養の最終8時間における取り込み量を液体シンチレーションカウンターを用いて評価した。なお、被験物質濃度は0.001%とした。結果を表3に示す。その結果、表3に示すように、本植物エキスはいずれも血管内皮細胞に対し、低毒性であった。

【0024】

【表3】

## 6

植物エキス	形態変化	DNA合成抑制率(%)
ハコベ草	特に無し	15
仙鶴草	特に無し	43
甘茶	特に無し	42
茵陳蒿	特に無し	10
甘遂	特に無し	0
カッコウ	特に無し	10
連銭草	特に無し	40
カミツレ	特に無し	0
千金子	特に無し	0
浮き草	特に無し	30
薄荷	特に無し	36
延命草	特に無し	33

【0025】実施例1

連銭草抽出物(固形分)500g、ヒドロキシプロピルセルロース800g、軽質無水ケイ酸200g、乳糖500g、結晶セルロース500g及びタルク500gを常法により直径9mm、重量200mgの錠剤とした。

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【0026】実施例2

ハコベ草抽出物(固形分)1000g、結晶セルロース1000g、乳糖1500g及び軽質無水ケイ酸200gを常法によりカプセル剤とした。

【0027】実施例3

カミツレ抽出物(固形分)200g、乳糖200g、ヒドロキシプロピルセルロース300g及びタルク15gを常法により顆粒剤とした。

【0028】実施例4

30 ハコベ草抽出物(固形分)1g、コレステロール0.5g、コレステリルイソステアレート1g、ポリエーテル変性シリコン1.5g、環状シリコン20g、メチルフェニルポリシロキサン2g、メチルポリシロキサン2g、硫酸マグネシウム0.5g、5%エタノール5g、カルボキシメチルキチン0.5g及び精製水(残量)を混合し、クリームとした。

【0029】実施例5

40 連銭草抽出物(固形分)3g、コレステリルイソステアレート3g、流動パラフィン10g、グリセリルエーテル1g、グリセリン10g及び白色ワセリン(残量)を混合し、軟膏とした。

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CELL ADHESION INHIBITORS

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CELL ADHESION INHIBITORS

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[There are no amendments to this patent.]

Claims

1. Cell adhesion inhibitors that contain as the active ingredient one or more types of plants or extracts thereof selected from among the group composed of *Stellaria neglecta*, *Agrimonia pilosa*, *Hydrangea macrophylla*, *Artemisia capillaris*, *Euphorbia kansui*, *Agastache rugosa*, *Glechoma hederacea*, *Matricaria chamomilla*, *Euphorbia lathyris*, *Spirodela polyrhiza*, *Mentha haplocalyx*, and *Isodon japonicus*.
2. Cancer metastasis inhibitors that contain as the active ingredient the plants or extracts thereof of Claim 1.
3. Antiallergy agents that contain as the active ingredient the plants or extracts thereof of Claim 1.
4. Immunosuppressants that contain as the active ingredient the plants or extracts thereof of Claim 1.

### Detailed explanation of the invention

[0001]

#### Industrial application field

The present invention relates to cell adhesion inhibitors, cancer metastasis inhibitors, antiallergy agents, and immunosuppressants that contain as the active ingredient plants or extracts thereof.

[0002]

#### Prior art

Steroidal drugs, arachidonic acid metabolites, compounds that suppress the production and release of chemical mediators such as histamine, and receptor antagonists have been widely used as anti-inflammatories. Metabolic antagonists such as azathioprin and mizoribine, steroids such as prednisolone, various antibodies, cyclosporin, and FK506 are used as immunosuppressants. Substances that are useful as cancer metastasis inhibitors have yet to be discovered.

[0003]

Research on various types of inflammation, immune response, and cancer metastasis has advanced in recent years on the molecular level and clarified that a common point in these conditions is intercellular adhesion such as that between leukocytes and vascular endothelial cells or between cancer cells and vascular endothelial cells. It is also becoming clear that inhibiting the expression of the cell adhesion molecules involved in adhesion themselves or preventing intercellular adhesion by masking the adhesive molecules would be effective in the treatment of the aforementioned conditions [Regulating the Expression of Adhesive Molecules and its Clinical Application (Medical View Co., 1991), Nature, Vol. 364, pp. 149-155 (1993), Science, Vol. 247, pp. 456-459 (1990), Annual Review Immunology, 1989, pp. 175-185, Trends in Glycoscience and Glycotechnology, Vol. 4, No. 19, pp. 405-414 (1992), Jikken Igaku, Vol. 10, No. 11, pp. 1402-1413 (1992), Jikken Igaku, Vol. 11, No. 16, pp. 2168-2175 (1993), Science, Vol. 255, pp. 1125-1127 (1992), etc.]. Adhesive molecules on the cell surface such as ICAM-1, ELAM-1, and VCAM-1 have been demonstrated to participate in intercellular adhesion [Annual Review Immunology, 1989, pp. 175-185, Kansen·Ensho·Meneki, Vol. 19(2), pp. 129-153 (1989), and Kansen·Ensho·Meneki, Vol. 24(3), pp. 158-165 (1994)].

[0004]

Antibodies to and ligands of the cell surface adhesive molecules, N-(fluorenyl-9-methoxycarbonyl)aminoacetic acid and 3-deazaadenosine are known as substances that suppress cell adhesion [Proc. Natl. Acad. Sci. USA, Vol. 88, pp. 355-359 (1991), Immunopharmacology, Vol. 23, pp. 139-149 (1992), J. Biological Chemistry, Vol. pp. 267(13), 9376-9382 (1992), and J. Immunology, Vol. 144(2), pp. 653-661 (1990)], but their potency has not been satisfactory.

[0005]

Problems to be solved by the invention

Therefore, the object of the present invention is to propose drugs that effectively suppress this cell adhesion, as well as antiallergy agents, immunosuppressants, and cancer metastasis inhibitors.

[0006]

Means to solve the problem

Given the above information, the present inventors investigated the cell adhesion-suppressing effect of various plant extracts and conducted many studies using cancer models. As a result, they attained the present invention by discovering that the plants listed below have an unexpectedly good cell adhesion-inhibiting effect and are useful as antiallergy agents, immunosuppressants, and cancer metastasis inhibitors.

[0007]

Specifically, the present invention proposes cell adhesion inhibitors, cancer metastasis inhibitors, antiallergy agents, and immunosuppressants that contain as the active ingredient one or more types of plants or extracts thereof selected from among *Stellaria neglecta*, *Agrimonia pilosa*, *Hydrangea macrophylla*, *Artemisia capillaris*, *Euphorbia kansui*, *Agastache rugosa*, *Glechoma hederacea*, *Matricaria chamomilla*, *Euphorbia lathyris*, *Spirodela polyrhiza*, *Mentha haplocalyx*, and *Isodon japonicus*.

[0008]

The plants used in the present invention are selected from among *Stellaria neglecta*, *Agrimonia pilosa*, *Hydrangea macrophylla*, *Artemisia capillaris*, *Euphorbia kansui*, *Agastache rugosa*, *Glechoma hederacea*, *Matricaria chamomilla*, *Euphorbia lathyris*, *Spirodela polyrhiza*, *Mentha haplocalyx*, and *Isodon japonicus*. The entire plant or the leaves, stems, branches, and

roots, etc., of these plants can be used in the present invention, as is or after drying or crushing, or extracts may be used.

[0009]

An example of the extraction technique is to extract a crushed product of all or part of the plant with water or an organic solvent, usually at 3-70°C. Organic solvents that can be used in extraction are not particularly limited and include hydrocarbons such as petroleum ether, cyclohexane, toluene, and benzene, halogenated hydrocarbons such as carbon tetrachloride, dichloromethane, and chloroform, ethers, esters such as ethyl acetate, ketones such as acetone, alcohols such as butanol, propanol, ethanol, methanol, polyethylene glycol, propylene glycol, and butylene glycol, and pyridine. The extraction solvents may be used individually or in mixtures of two or more types.

[0010]

These extracts may be used as they are or after treatment such as concentration, filtration, or freeze-drying as necessary. The extracts and plants may be used individually or in combinations of two or more types.

[0011]

The aforementioned plants and extracts thereof obtained as described above are excellent at suppressing cell adhesion as represented by adhesion between leukocytes and vascular endothelial cells. They also have excellent antiallergy effects, immunosuppressive effects, and cancer metastasis-inhibiting effects. Furthermore, they possess weak cytotoxicity and have little ability to irritate the skin and are therefore highly safe. Consequently, drugs that contain the aforementioned plants or extracts thereof as the active ingredient are useful in treating conditions such as periodontitis, rheumatism, bronchial asthma, pollinosis, psoriasis, impaired reperfusion after ischemia, acute respiratory distress syndrome, organ transplant rejection reactions, and autoimmune diseases, and in preventing cancer metastasis, based on the inhibition of cell adhesion.

[0012]

The content of the aforementioned plants or extracts thereof in the drugs is not particularly limited, but is usually 0.0001-40% by weight, preferably 0.01-20% by weight, calculated for the dry solids fraction. The dose is preferably set at 20-500 mg/kg/day. Administration may be by any route such as oral, rectal, or topical. Furthermore, these plants and their extracts are known to be highly safe.

[0013]

In addition to the aforementioned essential ingredients, the drugs of the present invention can be administered after combining them arbitrarily with existing drugs such as anti-inflammatories, antiallergy agents, and antihistamines.

[0014]

The drug form can be arbitrary. Examples include solid forms such as tablets, granules, powders, capsules, suppositories, and troches and liquid forms such as syrups, emulsions, soft gelatin capsules, creams, gels, pastes, sprays, and injections.

[0015]

The excipients and other additives used for these preparations are not particularly limited. Examples include solid substances such as lactose, kaolin, sucrose, crystalline cellulose, cornstarch, talc, agar, pectin, stearic acid, magnesium stearate, lecithin, and sodium chloride and liquid ones such as glycerin, peanut oil, polyvinylpyrrolidone, olive oil, ethanol, benzyl alcohol, propylene glycol, and water.

[0016]

The drugs of the present invention can be manufactured by the usual methods.

[0017]

Effects of the invention

The drugs of the present invention have low cytotoxicity and excellent cell adhesion-inhibiting effects, antiallergy effects, cancer metastasis-inhibiting effects, and immunosuppressive effects because they are derived from plants. Therefore, the drugs of the present invention can be widely used in the prevention and treatment of cancer, asthma, allergic rhinitis, pain, psoriasis, urticaria, rheumatism, pollinosis, periodontitis, impaired reperfusion after ischemia, acute respiratory distress syndrome, autoimmune diseases, and acute pulmonary disorders.

[0018]

Application examples

Next, the present invention will be explained in greater detail through application examples. However, the present invention is not limited to these examples. The plant extracts used in the application examples below were obtained by the following method. 1 kg of dry

*Stellaria neglecta* was extracted for 1 week at room temperature by 5 L of 70% ethanol to obtain a 70% ethanol-soluble fraction. A total of 10 L of extract was obtained by repeating the same procedure on the residue from which the extract had been separated. The solvent was evaporated from this extract solution and 85 g of extract was obtained by drying under reduced pressure. Extracts were also obtained from the other plants by the same procedure.

[0019]

#### Application Example 1

The plant extracts shown in Tables 1-3 below were obtained by the aforementioned method. These plant extracts were supplied for the following study.

(1) Test of inhibition of cell adhesion between leukocytes and vacular endothelial cells:

The test substance was added to make a final concentration [% by weight calculated based on the dry solids fraction] (the same hereinafter) of 0.001% to human vascular endothelial cells that had become confluent on 96-well culture plates. After 18 h, human IL-1 $\alpha$  was added to make a final concentration of 2.5 ng/mL and cultured for 6 h. After removing the culture solution and washing twice with fresh culture solution, 200  $\mu$ L of  $^{51}\text{Cr}$ -labeled human peripheral blood leukocytes (10 cells/mL) were added and cultured. 30 min later, the unadhered cells were removed and the radioactivity was measured after dissolving the adhering cells. Table 1 shows the results.

*Stellaria neglecta*, *Agrimonia pilosa*, *Hydrangea macrophylla*, *Artemisia capillaris*, *Euphorbia kansui*, *Agastache rugosa*, *Glechoma hederacea*, *Matricaria chamomilla*, *Euphorbia lathyris*, *Spirodela polyrhiza*, *Mentha haplocalyx*, and *Isodon japonicus* were judged, based on these results, to have excellent cell adhesion-inhibiting activity.



[0020]

Table 1

Plant extract	Leukocyte adhesion inhibition index (%)
<i>Stellaria neglecta</i>	90
<i>Agrimonia pilosa</i>	95
<i>Hydrangea macrophylla</i>	81
<i>Artemisia capillaris</i>	82
<i>Euphorbia kansui</i>	95
<i>Agastache rugosa</i>	79
<i>Glechoma hederacea</i>	95
<i>Matricaria chamomilla</i>	72
<i>Euphorbia lathyris</i>	87
<i>Spirodela polyrhiza</i>	80
<i>Mentha haplocalyx</i>	91
<i>Isodon japonicus</i>	85

[0021]

(2) Test of inhibition of cell adhesion between cancer cells and vascular endothelial cells:

The test substance was added to make final concentrations of 0.001 and 0.0001% to human vascular endothelial cells that had become confluent on 96-well culture plates. After 18 h, human IL-1 $\alpha$  was added to make a final concentration of 2.5 ng/mL and cultured for 6 h. After removing the culture solution and washing twice with fresh culture solution, 200  $\mu$ L of  $^{51}$ Cr-labeled human myeloma cells (HL-60, 10 cells/mL) were added and cultured. After 30 min, the unadherent cells were removed and the radioactivity was measured after dissolving the adhering cells. The results are shown in Table 2. *Stellaria neglecta*, *Agrimonia pilosa*, *Hydrangea macrophylla*, *Artemisia capillaris*, *Euphorbia kansui*, *Agastache rugosa*, *Glechoma hederacea*, *Matricaria chamomilla*, *Euphorbia lathyris*, *Spirodela polyrhiza*, *Mentha haplocalyx*, and *Isodon japonicus* were judged, based on these results, to strongly inhibit adhesion of cancer cells and vascular endothelial cells, which is important in the metastasis of cancer cells.

[0022]

Table 2

Plant extract	0.001%	0.0001%
	Cancer cell adhesion inhibition index (%)	
<i>Stellaria neglecta</i>	92	48
<i>Agrimonia pilosa</i>	98	27
<i>Hydrangea macrophylla</i>	80	5
<i>Artemisia capillaris</i>	84	10
<i>Euphorbia kansui</i>	94	64
<i>Agastache rugosa</i>	82	5
<i>Glechoma hederacea</i>	98	30
<i>Matricaria chamomilla</i>	76	5
<i>Euphorbia lathyris</i>	78	38
<i>Spirodela polyrhiza</i>	84	3
<i>Mentha haplocalyx</i>	97	8
<i>Isodon japonicus</i>	82	5

[0023]

## (3) Test of toxicity to vascular endothelial cells (cell morphology, DNA synthesis):

Changes in cell morphology were evaluated visually by inversion microscope. DNA synthesis was evaluated using  $^3\text{H}$ -thymidine uptake as the indicator by the usual method by measuring the uptake by liquid scintillation counter in the last 8 h of a 24 h culture after adding the test substance. The concentration of the test substance was set at 0.001%. The results are shown in Table 3. As can be seen in Table 3, these results demonstrated that the plant extracts all had low toxicity for vascular endothelial cells.

[0024]

Table 3

Plant extract	Changes in morphology	DNA synthesis inhibition index (%)
<i>Stellaria neglecta</i>	none in particular	15
<i>Agrimonia pilosa</i>	none in particular	43
<i>Hydrangea macrophylla</i>	none in particular	42
<i>Artemisia capillaris</i>	none in particular	10
<i>Euphorbia kansui</i>	none in particular	0
<i>Agastache rugosa</i>	none in particular	10
<i>Glechoma hederacea</i>	none in particular	40
<i>Matricaria chamomilla</i>	none in particular	0
<i>Euphorbia lathyris</i>	none in particular	0
<i>Spirodela polyrhiza</i>	none in particular	30
<i>Mentha haplocalyx</i>	none in particular	38
<i>Isodon japonicus</i>	none in particular	33

[0025]

Application Example 1 [sic]

500 g of *Glechoma hederacea* extract (solids fractions), 800 g of hydroxypropyl cellulose, 200 g of soft silicic anhydride, 500 g of lactose, 500 g of crystalline cellulose, and 500 g of talc were made into tablets 9 mm in diameter and weighing 200 mg by the usual method.

[0026]

Application Example 2

1000 g of *Stellaria neglecta* extract (solids fraction), 1000 g of crystalline cellulose, 1500 g of lactose, and 200 g of soft silicic anhydride were made into capsules by the usual method.

[0027]

Application Example 3

200 g of *Matricaria chamomilla* (solids fraction), 200 g of lactose, 300 g of hydroxypropyl cellulose, and 15 g of talc were made into granules by the usual method.

[0028]

Application Example 4

1 g of *Stellaria neglecta* extract (solids fraction), 0.5 g of cholesterol, 1 g of cholesteryl isostearate, 1.5 g of polyether-modified silicone, 20 g of cyclic silicone, 2 g of methyl phenyl polysiloxane, 2 g of methyl polysiloxane, 0.5 g of magnesium sulfate, 5 g of 55% ethanol, 0.5 g of carboxymethyl chitin, and purified water (remainder) are mixed to make a cream.

[0029]

Application Example 5

3 g of *Gleochoma hederacea* extract (solids fraction), 3 g of cholesteryl isostearate, 10 g of liquid paraffin, 1 g of glyceryl ether, 10 g of glycerin, and white petrolatum (remainder) were mixed to make an ointment.